Remarks

Claim 34 was amended to define a therapeutic system comprising a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2, at intracellular sites where NQO2 is expressed. Support for the amendment is found, for example, on page 46, lines 19-21.

Rejection Under 35 U.S.C. § 103

Claims 34, 41-44, and 48 were rejected under 35 U.S.C. § 103(a) as obvious over Friedlos *et al., Biochem. Pharmacol.*, 44, 1739-1743, (1992) ("Friedlos #1"), in combination with Norris *et al., Can. J. Chem.*, Vol. 55, 1687-1695 (1977) ("Norris") in view of Friedlos *et al., Biochem. Pharmacol.,* 44, 25-31, (1992) ("Friedlos #2") and Jaiswal, *J. Biol. Chem.*, 269, 14502-14508, (1994) ("Jaiswal"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Legal Standard

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999).

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

Analysis

Claim 34 was amended to recite a therapeutic system comprising a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 at intracellular sites and a compound of formula I. Support for the amendment is found, for example, on page 46, lines 19-21.

a. Friedlos et al., Biochem. Pharmacol., 44, 1739-1743, (1992) ("Friedlos #1")

Friedlos #1 describes reduced pyridine nucleotides as cofactors in the reduction of CB 1954 by the enzyme DT diaphorase (NQO1) (abstract). Friedlos #1 does not disclose or suggest the enzyme NQO2. Friedlos #1 is concerned with the use of reduced pyridinium nucleotides as cofactors for the reduction of CB 1954 by DT diaphorase. Friedlos #1 does not disclose or suggest that the combination of an analogue of NRH and CB 1954, as claimed, could be used as a system for any type of therapy, let alone the treatment of tumors which express NQO2.

b. Norris et al., Can. J. Chem., Vol. 55, 1687-1695 (1977) ("Norris")

Norris describes the identification and synthesis of pyridinium and dihydropyridine compounds which do not contain the adenine nucleotide portion of NADH (page 1687, 2nd column, 1st paragraph and Table 3). Norris describes the stability of a series of substituted pyridinium ions and their 1,4-dihydro reduction products in aqueous buffers. Norris does not disclose or suggest that the combination of an analogue of NRH and CB 1954, as claimed, could be used as a system for any type of therapy let alone the treatment of tumors which express NQO2.

c. Friedlos et al., Biochem. Pharmacol., 44, 25-31, (1992) ("Friedlos #2")

Friedlos #2 describes reduced pyridinium derivatives as synthetic cofactors in the reduction of CB 1954 by the enzyme DT diaphorase (NQO1). (page 28, 1st column, last paragraph and Table 1). Friedlos #2 does not disclose or suggest that the combination of an analogue of NRH and CB 1954, as claimed, could be used as a system for any type of therapy,

much less the treatment of tumors which express NQO2.

d. Jaiswal, J. Biol. Chem., 269, 14502-14508, (1994) ("Jaiswal")

Jaiswal describes the gene structure, activity, and tissue-specific expression of NQO2. Jaiswal alleges that the protein encoded by the NQO2 gene catalyzes the 4-nitroreduction of the anti-tumor compound CB10-200 with almost equal efficiency as NQO1 (DT diaphorase), which suggests that NQO1 and NQO2 have comparable nitroreductase activities (page 14506, paragraph bridging columns 1 and 2).

e. Friedlos #1 in combination with Norris in view of Friedlos #2 and Jaiswal

The claims are directed to a therapeutic system which has as its basis the finding that NQO2 can rapidly reduce CB1954 and that NQO2, not NQO1, is responsible for the potentiating effects of the claimed NRH analogues on CB1954 toxicity towards human cells (see page 8, lines 18-21 in the published PCT application). This would not have been obvious to a person skilled in the art from the disclosure in the cited references.

Friedlos #1, Friedlos #2 and Norris do not relate to NQO2

Friedlos #1 and Friedlos #2 do not disclose or suggest NQO2. In fact, these documents predate the discovery of NQO2. Therefore, one of ordinary skill in the art would not be motivated to combine these references with Jaiswal, which relates to a different enzyme, NQO2.

Friedlos #2 discloses that NADH is the only suitable cofactor for CB 1954 and that in vivo no other cofactor would be effective.

The stimulation of CB 1954 cytotoxicity by NRH in human cells described in Friedlos #1 is specifically ascribed to NQO1 (DT diaphorase) because of the metabolism of NADH (which cannot cross cell membranes) into NRH (which can cross cell membranes). This is even stated in the title of the paper.

Friedlos #1 states at page 1742, right column, lines 57-65 that "*we have shown that NRH is a cofactor for DT diaphorase,* ***but not for another enzyme examined…****and it is unlikely to be a cofactor for the majority of enzymes that are obligate for either NADH or NADPH. It would appear therefore that NADH (in the presence of serum) is enhancing the rate of reduction of CB 1954 by providing NRH,* ***an additional DT diaphorase-specific cofactor****".*

There is nothing in Norris to suggest that the compounds might be cofactors for NQO1, let alone NQO2. Norris does not disclose the elements missing from Friedlos #1 and Friedlos #2.

NQO1 and NQO2 are different enzymes

The Examiner has assumed that all co-substrates for the enzyme NQO1 (DT diaphorase) will work equally well for NQO2. This assumption is not correct. NQO2 **cannot** use NADH as a co-substrate to reduce CB 1954, unlike *E. coli* nitroreductase and DT diaphorase (NQO1) (see page 76, line 28 to page 77, line 5 in the present application).

Jaiswal does not disclose that NQO1 and NQO2 have comparable reductase activities for all co-substrates and substrates. In fact, Jaiswal discloses that NQO2 lacks the quinone-reductase activity characteristic of NQO1 (see page 14502, right column lines 28-30 which states

that NQO1, **but not NQO2**, effectively metabolizes 2,6-dichlorophenolindophenol and menadione). Thus, NQO2 is a different enzyme with different properties and therefore there can be no expectation that co-substrates for NQO1 will necessarily work with NQO2.

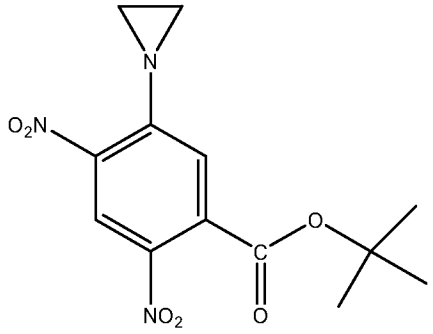
At the time of the applicants' priority date, there was a known biochemical distinction between NQO1 and NQO2. Furthermore, although Friedlos #2 discloses that the co-factor requirements for NQO1 may be lax, this is disclosed in relation to NQO1 and menadione, **not** NQO2 and CB 1954. Menadione is not effectively metabolized by NQO2.

The data in Friedlos #2 relating to CB 1954 is an artifact, as evidenced by Friedlos #2 stating that only NADH is a suitable co-factor *in vivo*. Friedlos #2 indicates that the apparent K_m values for all of the cofactors with CB 1954 appeared to be approaching zero so that nicotinamide ribotide was apparently just as good a co-factor for the reduction of CB 1954 as NADH (page 29, right column, first full paragraph, final five lines). However, due to the particular kinetics underlying the operation of DT diaphorase, the K_m values are actually an artifact (page 30, left column, line 25 to page 30, second column, line 1). Thus, not all of the cofactors, in reality, have the same activity. This is demonstrated by using a mixture of NADH and nicotinamide ribotide wherein all of the NADH is oxidized preferentially over nicotinamide ribotide during the reduction of CB 1954 (page 30, left column, line 25 to page 30, second column, line 1). Therefore, there is no disclosure or suggestion in Friedlos that the simplest quaternary derivatives would actually be as effective as NADH for the reduction of CB 1954 in the presence of DT diaphorase, let alone NQO2. This is consistent with the disclosure in

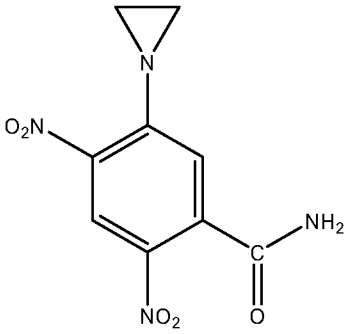
Friedlos #1 which is that only NADH (which is converted to NRH) would be a suitable co-factor for CB 1954. NADH is not a co-factor for the reduction of CB 1954 by NQO2. Friedlos #1 and #2 actually teach away from the claimed therapeutic systems by suggesting the use of NADH for the reduction of CB 1954.

Structural Differences Between CB10-200 and CB 1954

Jaiswal does not disclose or suggest that NQO2 would be able to activate CB 1954 in the presence of the specified co-factors. Jaiswal only mentions the anti-tumor compound CB10-200, not CB 1954. Jaiswal also does not disclose or suggest that co-factors other than NADH could be used with CB10-200. A comparison of the structures of CB10-200 and CB 1954 is shown below.



CB10-200



CB 1954

CB10-200 and CB 1954 have distinct structural differences. CB10-200 contains an ester functionality (-O-tBu), while CB 1954 contains an amide functionality ($-NH_2$). One of ordinary skill in the art would recognize the differences in the electronic effects (nitrogen v. oxygen) and steric effects (NH_2 vs. O-tBu) of the amide group vs. the ester group. In fact, the Examiner has previously stated that it cannot be predicted which prodrugs could be converted into cytotoxic

drugs by the action of NQO2 (see the Office Action mailed July 23, 2004, page 4, final paragraph). In view of this uncertainity, one or of ordinary skill in the art would not have an expectation of success for the activation of CB1954 by NQO2 based only on the disclosure of CB10-200 in Jaiswal.

f. Conclusion

One of ordinary skill in the art would not be motivated to combine the references cited by the Examiner to arrive at the claimed therapeutic systems. The Examiner using hindsight to extrapolate the fact that NQO1 can use co-factors other than NAD(P)H to NQO2. Friedlos #1, Norris, and Friedlos #2 do not disclose or suggest NQO2. NQO1 and NQO2 are different enzymes, which is supported by experimental data. For NQO1, no cofactor is superior to NAD(P)H with respect to the rate of reduction achieved or kinetic constants such as K_m. This is not the case for NQO2, where NRH and other claimed analogues of NRH are greatly superior to NADH in both of these respects. This could not have been predicted from the references cited by the Examiner. Therefore, the claims, as amended, are not obvious over Friedlos #1 in combination with Norris in view of Friedlos #2 and Jaiswal.

Allowance of claims 34, 41-44, and 48, as amended, is respectfully solicited.

Respectfully submitted,

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